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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,890	12/29/2004	Briony Forbes	A20-073	9372

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EXAMINER	
BORGEEST, CHRISTINA M	
ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,890	FORBES, BRIONY	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-39 and 42-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-39,42-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Applicants amendment filed 30 April 2007 is acknowledged. Claims 1-36 and 4-41 are cancelled. Claims 37 and 42 are amended. Claims 67-68 are new

Election/Restrictions

Upon further consideration, the species election requirement set forth at pages 2-3 of the Restriction requirement mailed 13 March 2006 is hereby withdrawn. In addition, the Office action mailed 8 August 2006 is hereby vacated and the rejections therein are withdrawn, and a new office action follows immediately below. Because the Remarks filed by Applicants on 30 April 2007 are directed to rejections that are no longer of record, they will not be addressed herein. Claims 37-39 and 42-68 are under examination.

Claim Objections

Claim 67 is objected to because of the following informalities: "(New)" is written twice. Appropriate correction is required.

Claim 68 is objected to because of the following informalities: There is no period at the end of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 37-39, 42-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 46, 50 and 67 recite "able to effect binding of," which is unclear. Claims 37-39, 42-45, 47-49, 41-66 and 68 are rejected for depending upon indefinite claims. This rejection could be overcome by changing "able to effect binding of" to "able to bind."

Claims 37-39, 42-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 46 and 67 recite "on contact with an extracellular matrix (ECM)," which is indefinite because it is not clear what is contacting the ECM. Claims 37-39, 42-45, 47-49, 41-66 and 68 are rejected for depending upon indefinite claims. This rejection could be overcome by changing "on contact with an extracellular matrix (ECM)" with "on contact of said altered human IGFBP-2 molecule with an extracellular matrix (ECM)."

Claim Rejections - 35 USC § 112, first paragraph – Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42-47, 67 and 68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an altered human IGFBP-2 able to bind IGF-I or IGF-II with high affinity wherein an inhibited release of IGF occurs on contact of said altered human IGFBP-2 molecule with an extracellular matrix (ECM), wherein said altered IGFBP-2 is the double mutant K180A K181A or the single mutants K227A, K234A, K237A or the deletion mutant Des(114-170) as shown in Tables 2 and 3 (p. 20-21, respectively) of the specification, does not reasonably provide enablement for the claims as broadly recited. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 Fed. Cir. 1988) These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The prior art is silent with respect to these mutations with the recited activity limitations and thus unpredictable, so one of ordinary skill in the art must rely upon the

amount of direction given by the inventor and the existence of working examples for guidance. The specification teaches only altered human IGFBP-2 molecule with an extracellular matrix (ECM), wherein said altered IGFBP-2 is the double IGFBP-2 mutant K180A K181A or the single mutants K227A, K234A, K237A or the deletion mutant Des(114-170) (see Tables 2 and 3) were tested for the ability to bind IGF-I and IGF-II. In addition, the recited phrases, "having an alteration" (claims 67 and its dependents) and "comprising a deletion" (claims 45, 50 and dependents) are infinitely broad as there is no positive recitation of what structures must be present in order to have the recited functions.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of five substitutions and deletions (as shown in Tables 2 and 3 of the specification) to

enable one of ordinary skill in the art to determine, without undue experimentation, the other positions in the IGFBP-2 which are tolerant to change, and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Due to the large quantity of experimentation necessary to generate the infinite number of IGFBP-2 muteins recited in the claims and screen them for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the

breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 37-39 and 58-66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing IGF-mediated proliferation in MCF-7 cells, the method including the step of contacting said cells with the IGFBP-2 double mutant K180A K181A or the IGFBP-2 single mutants K227A, K234A, K237A or the IGFBP-2 deletion mutant Des(114-170) or alternatively, a method of reducing IGF-mediated proliferation in HT29, CaCo and T84 cells, the method including the step of contacting said cells with the IGFBP-2 deletion mutant Des(114-170), does not reasonably provide enablement for the methods as broadly recited. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 Fed. Cir. 1988) These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the

existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. The art concerning the treatment of cancer with IGFBP-2 is extremely complex and unpredictable. The preponderance of the literature teaches that IGFBP-2 is associated with an increased cell proliferation in cancer cell lines (see Eiseman et al., Clin Cancer Res. 2007; 13: 2121-2127, p. 2121, right column, 1st paragraph). In addition, increased levels of IGFBP-2 are found in prostate, Wilm's and CNS tumors (see p. 815, left column, last paragraph through entire right column in Rajaram et al., Endocr Rev 1997;18: 801-31, p. 815, left column, last paragraph). Notably, it is taught that elevation of IGFBP-2 in patients with CNS tumors may be due to production of IGFBP-2 by the tumor itself (see Rajaram et al., p. 815, right column, last paragraph), thus this does not support enablement for the claimed methods in any population of cells. Boulle et al. (J Clin Endocrinol Metab 1998; 83: 1713-20) teach that "IGFBP-2 may be a regulator of the proliferative effects of IGF-II in [the adrenocortical] model" (see p. 1719, left column, last paragraph). Moore et al. (Int J Cancer. 2003: 105: 14-19) teach that IGFBP-2 may play an active role in the progression of prostate cancer (see abstract; p. 18, right column, last paragraph), and suggest that a possible mechanism for this is the "activation or inactivation of a regulatory switch" that leads to IGFBP-2 promoting carcinogenesis (p. 16, Figs. 2 & 3; p. 18, right column, last paragraph). Given the strong teaching in the literature that IGFBP-2 promotes cancerous growth in prostate cancer cells, this does not support enablement for reducing IGF mediated proliferation in prostate cancer by administration of the IGFBP-2 muteins of the instant invention. Regarding MCF-7 cells,

Kibbey et al. (Mol Pharmacol 2006;69: 833-45) teach that in spite of the reported proliferative role of IGFBP-2 in cancer cell lines, IGFBP-2 ameliorated cell growth in MCF-7 cells (see p. 838, right column, Figure 3), and further teach that "[the] lack of complete blockade of IGF-1 action [by IGFBP-2] may be because of proteolysis of IGFBP-2 by proteinases expressed by MCF-7 cells (p. 833, left column, penultimate paragraph). Given the teaching in the literature regarding MCF-7 cells, the specification is enabling for a method of reducing IGF-mediated proliferation in MCF-7 cells, the method including the step of contacting said cells with the IGFBP-2 double mutant K180A K181A or the IGFBP-2 single mutants K227A, K234A, K237A or the IGFBP-2 deletion mutant Des(114-170), but not to the methods as broadly claimed.

The claims encompass treatment of cancer, which is a difficult and complex problem. Testing the huge number of different IGFBP-2 muteins encompassed by the claims (see previous scope of enablement rejection) for the ability to treat cancer would require undue experimentation by one of ordinary skill in the art. Given the extreme unpredictability in the art with respect to the treatment of any cancerous cell population and the amount of experimentation that would require testing all the encompassed IGFBP-2 muteins, one of ordinary skill in the art must turn to the specification for guidance. Regarding the treatment of cancer, the specification is silent. The specification teaches that of the five IGFBP-2 mutants tested (double mutant K180A K181A or the single mutants K227A, K234A, K237A or the deletion mutant Des(114-170)), only the IGFBP-2 deletion mutant Des(114-170) showed any resistance to proteolysis and only in PC3, HT29, CaCo and T84 cells (see p. 22, Table 4 and 2nd

paragraph of the specification and Figure 5). The other IGFBP-2 muteins (double mutant K180A K181A and the single mutants K227A, K234A, K237A) were tested in the T84 cell line, but none were found resistant to proteolysis (p. 23, 1st paragraph of the instant specification). According to Boulle et al., one of the possible mechanisms suggested for the increased proliferative effects of IGFBP-2 in the adrenocortical model is proteolysis (see p. 1718, right column, last paragraph to p. 1719, 1st paragraph):

> Proteolysis is another possible mechanism for regulating IGFBP-2/IGF-II interactions...IGFBP-2 proteolysis indeed occurred in adrenocortical tumor extracts, and large amounts of the IGFBP-2 proteolytic fragment were present in malignant tumors. By decreasing IGF-II affinity, IGFBP-2 proteolysis may increase IGF-II bioavailability and enhance its proliferative effects on adrenocortical tumor cells.

Given the teaching in the literature that proteolysis might be a mechanism for IGFBP-2 promotion of tumor growth, a showing in the specification that the Des(114-170) mutant was resistant to proteolysis in certain cell lines supports enablement for a method of reducing IGF-mediated proliferation in HT29, CaCo and T84 cells, the method including the step of contacting said cells with the IGFBP-2 deletion mutant Des(114-170), but not to the methods as broadly claimed.

Due to the large quantity of experimentation necessary to make and test all the encompassed IGFBP-2 muteins for the ability to reduce IGF mediated proliferation of cancerous cells, the lack of direction/guidance presented in the specification and the absence of working examples directed to the same, the complex nature of the invention, the contradictory state of the prior art and the unpredictability of the art with respect to the role of IGFBP-2 in promoting cancer and the lack of evidence of its role in inhibition of cancerous cells (see the discussion above and the cited references), (the level of skill

of those in the art,) the unpredictability of the effects of mutation on protein structure and function (see previous scope of enablement with respect to breadth of the recited IGFBP-2 mutants, which is also directly relevant to the claimed methods), and the breadth of the claims which fail to recite adequate positive structural limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, first paragraph – Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42-57, 67 and 68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of particular

substitution and deletion mutants, however, there is no identification of any particular portion of the remaining IGFBP-2 structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the double IGFBP-2 mutant K180A K181A or the single IGFBP-2 mutants K227A, K234A, K237A or the IGFBP-2 deletion mutant Des(114-170) as shown in Tables 2 and 3 (p. 20-21, respectively), the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to

be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated altered IGFBP-2 molecules described as the double mutant K180A K181A or the single mutants K227A, K234A, K237A or the deletion mutant Des(114-170) as shown in Tables 2 and 3 (p. 20-21, respectively), but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is 571-272-4482. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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